Right medial temporal–lobe contribution to object–location memory

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Right medial temporal-lobe contribution to object-location memory

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SUMMARY

An important aspect of normal human memory, and one humans share with many other species, is the ability to remember the location of objects in their environment. There is by now strong evidence from the study of epileptic patients undergoing brain surgery that right temporal-lobe lesions that encroach extensively upon the hippocampal and parahippocampal gyrus impair the delayed, but not the immediate, recall of the location of objects within a random array. These findings have now been extended to a multiple-trial, spatial-array learning task; by including not only patients tested after unilateral anterior temporal lobectomy but also those with a selective left or right amygdalohippocampectomy, it has been shown that the deficits associated with right hippocampal lesions are not dependent upon conjoint damage to the lateral temporal neocortex. Furthermore, the fact that on the learning task no group differences were seen on Trial 1, at zero delay, strengthened the view that the impairment was in the maintenance and subsequent retrieval of information rather than in its initial encoding. These results left unresolved the question of whether the deficit was in the mediation of object–place associations or whether it could be reduced to a more general impairment in memory for location as such. Also left unanswered was the neuroanatomical question as to the relative contributions of the hippocampus and the parahippocampal gyrus to the performance of the experimental tasks. These questions were addressed in two blood-flow activation studies that made use of positron emission tomography (PET) and magnetic resonance imaging (MRI) and incorporated computerized versions of object-location and simple-location memory tasks. Taken together, the results point to a special contribution from the anterior part of the right parahippocampal gyrus, probably corresponding to the entorhinal cortex, to the retrieval of object–place associations, a result consonant with neurophysiological findings in non-human primates.

1. INTRODUCTION

The study of patients undergoing unilateral brain operations for the relief of epilepsy has revealed impairments after right anterior temporal lobectomy on a variety of spatial learning and spatial memory tasks, but only if the removal encroached extensively upon the hippocampus and/or the parahippocampal gyrus. The tasks sampled ranged from simple delayed recall of the position of a point on a line (Corsi 1972; Rains & Milner 1994) to more complex ones, such as stylus maze learning, both visual (Milner 1965) and tactual (Corkin 1965), and spatial conditional associative learning (Petrides 1985). These results for spatial memory are in marked contrast to the findings for complex visual patterns, such as faces, abstract designs, or the figurative detail in representational drawings, where an impairment in recognition memory is demonstrable after right temporal-lobe removals even when the hippocampal region is spared (Kimura 1963; Milner 1968; Burke & Nolan 1988; Pigott & Milner 1993). They also contrast with those for verbal material, where memory impairment is typically seen after left temporal lobectomy but not after right.

The domain of spatial memory is broad and heterogeneous. This paper will focus on one conspicuous aspect, namely the ability to remember the location of objects in the environment. In what follows, findings are presented from lesion studies in patients and from positron emission tomography (PET) studies in normal volunteers to examine the contribution of the right hippocampal region to the processes underlying object-location memory.

2. LESION STUDIES: THE RECALL OF THE LOCATION OF OBJECTS IN AN ARRAY

Smith & Milner (1981, 1984, 1989) have demonstrated a clear impairment after right temporal lobectomy on a task requiring the recall, after an interval of 4 min, of the locations of 16 toy objects within an array, the occurrence of the deficit being contingent upon inclusion of the bulk of the hippocampus and/or parahippocampal gyrus in the removal. No impairment was seen after corresponding removals from the left temporal lobe, nor after large frontal-lobe removals from either hemisphere. Notably, the impairment of the right temporal-lobe group with extensive hippocampal lesions (RTH) was manifested in both a greater than average displacement of each object from its original position (its absolute location) and an impaired recall of each object's position relative to its neighbours (its relative location). The presence of an intratrial interval was, however, critical in eliciting the deficit: at zero delay all groups performed normally, thus showing that the impaired recall after 4 min was due to rapid forgetting of information that had been accurately perceived.

Crane *et al.* (1995) have since extended Smith & Milner's findings to a learning paradigm, in which subjects were first instructed to name and remember the locations of 12 objects randomly distributed in fixed positions on a board. The array was then removed from view, and the subjects were given an identical set of objects and required to place them in the corresponding positions on an empty board. Placements that fell within a radius of 5 cm of the target position were judged correct, and the subjects were informed as to the total number correct on that trial. This process was repeated over successive trials, with an intertrial interval of 2–3 min, until all 12 items had been correctly placed on a given trial, or until 10 trials had been completed.

This study broke new ground by including not only patients tested after left or right temporal lobectomy, but also those who had undergone a selective left or right amygdalohippocampectomy (LAH or RAH), sparing the lateral and polar temporal neocortex and thus permitting more direct observations of the effect of the medial temporal-lobe lesion on task performance. Figure 1 displays the mean trials to criterion for the various temporal-lobe subgroups and for a normal control group (NC) matched to the patient group with respect to age and education. Subsequent analysis showed both the RTH and RAH groups to be impaired relative to the NC group but not to differ from one another. In contrast to their impaired learning over multiple trials, the RTH and RAH groups performed normally on the first recall trial. It seems probable, therefore, in the light of Smith & Milner's findings, that their impaired learning stems from abnormally rapid forgetting during the 2–3 min intertrial intervals.

These findings for the human right hippocampal region accord well with the results of lesion studies in the monkey, where both bilateral hippocampectomy (Parkinson *et al.* 1988) and fornix transection (Gaffan & Saunders 1985; Gaffan & Harrison 1989) have been shown to impair the acquisition and retention of object–place associations. The present authors' own findings are also consistent with those models of hippocampal function that emphasize the role of this structure in spatial memory, notably the cognitive map hypothesis of O'Keefe & Nadel (1978) and the personal memory hypothesis of Gaffan & Harrison (1989). Nevertheless, several important questions remain to be addressed. First, it is not clear whether the right hippocampal system is critically involved in mediating associations between object and place, or whether the impairment observed on object-location memory tasks after right hippocampal lesions can be reduced to a deficit in memory for location as such. It is also not clear, from a neuroanatomical standpoint, whether damage to the hippocampus itself is responsible for the deficits seen, or whether the parahippocampal gyrus plays an equal or preponderant role in the performance of the selected tasks. Blood-flow activation studies were therefore undertaken in normal subjects, with the use of positron emission tomography (PET) and magnetic resonance imaging (MRI), in an attempt to resolve these issues.

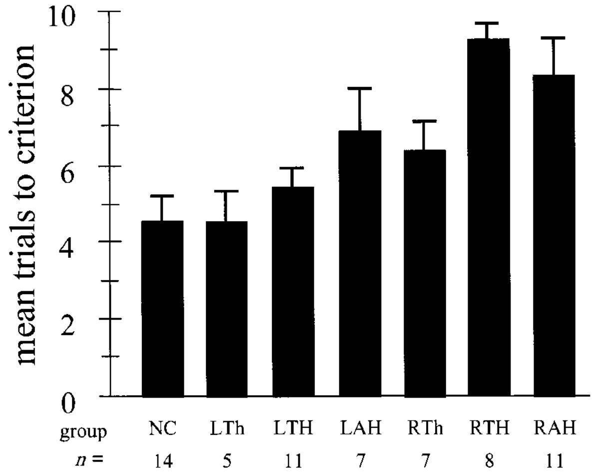

Figure 1. Spatial-array learning: the number of trials required to reach criterion. Each subject was tested on two arrays; the mean trials-to-criterion value given is an average for these two tests. NC, normal control; LTh, left temporal-lobe resection, small hippocampal removal (< 1.5 cm); LTH, left temporal-lobe resection, large hippocampal removal; LAH, left selective amygdalohippocampectomy; RTh, RTH, RAH, groups of patients with corresponding resections from the right temporal lobe. Error bars give the standard error of the data. Compared with NC subjects, performance was significantly impaired in the RTH and RAH groups.

3. PET STUDIES OF OBJECT-LOCATION MEMORY

In the following two experiments, the relative distribution of cerebral blood flow (CBF) was measured by using the bolus $H_2{}^{15}O$ method with averaged image subtraction (Raichle *et al.* 1983; Fox *et al.* 1985). A high-resolution MR image was obtained for each subject and co-registered with the corresponding PET images; each matched pair of MR and PET data sets was linearly transformed into stereotaxic space (Collins *et al.* 1994; Talairach & Tournoux 1988). The PET data were normalized for global differences in CBF and the mean CBF-change image volumes were obtained. The presence of significant focal changes was tested according to the method of Worsley *et al.* (1992).

(*a*) *Object-location memory versus memory for simple location*

In this first PET study (Owen *et al.* 1996), 12 normal volunteers were scanned while performing a computerized version of the object-location memory task, which first required them to monitor and encode the positions of eight representational drawings of

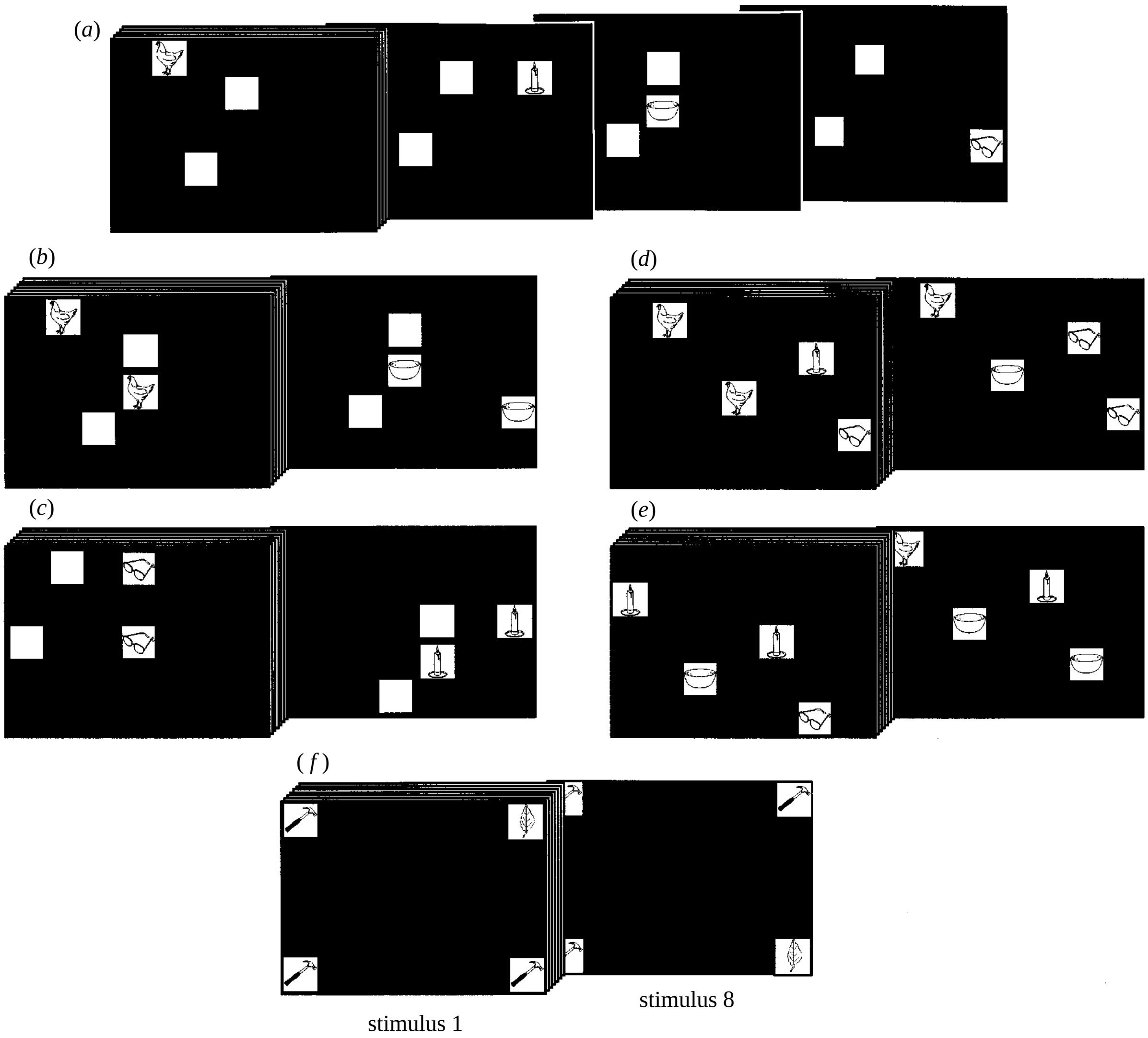

Figure 2. Object-location memory: shifted array versus fixed array. Schematic drawings showing examples from experimental tasks. (*a*) *Encoding object-locations* (10 min before first scan); (*b*) *Retrieval of fixed-array location using landmark cues*; (*c*) *Retrieval of shifted-array location using landmark cues* (the subject selects the correct location for that object relative to the landmarks); (*d*) *Retrieval of fixed-array location using object cues* (the subject selects the correct position of the duplicated object relative to the two other objects); (*e*) *Retrieval of shifted-array location using object cues*; (*f*) *Visuomotor control task* (subject touches the screen).

common objects, presented successively on a computer touch screen. Retrieval was tested in a separate scanning condition, eight minutes later, in which they had to select, from two alternatives, the correct location for each of these objects. In two analogous conditions, designed to look at memory for location alone, the subjects were required to encode, and then to retrieve, eight distinct locations represented by identical white boxes on the computer screen.

It was predicted that, when blood-flow in either of the location conditions was subtracted from that in the corresponding object-location condition, activation would be seen in the ventral visual pathway (Ungerleider & Mishkin 1982), brought about by the introduction of representational drawings as compared with empty boxes. This was borne out by the results, as illustrated for *Encoding* in figure 3*a*, which shows, in sagittal section, significant activation in the anterior fusiform gyrus and the prestriate cortex bilaterally when blood flow in the *Encoding location* condition was subtracted from that in the *Encoding object-location* condition.

The second prediction, and the motive for the study, was that increased blood-flow in the right hippocampal region should also be seen when activation in the *Retrieving location* condition was subtracted from that in the *Retrieving object-location* condition, if this region were indeed critically involved in memory for object–place associations. This prediction was partly confirmed: although no changes were elicited in the hippocampus itself, an increase in blood flow was seen in the anterior part of the right parahippocampal gyrus (corresponding to the entorhinal cortex), as shown in coronal section in figure 3*b*. The fact that no such change was seen in the *Encoding* subtraction is consistent with the finding that patients with right-hippocampal lesions show normal recall of object-location at zero intratrial delay.

The negative findings for the hippocampus itself do not conflict with the notion that this structure is critically involved in spatial memory. In this particular study, as Owen *et al.* (1996) point out, all four scanning conditions involved memory for spatial information, the neural correlates of which may well have been subtracted out, leaving only those changes in blood flow specifically related to memory for the location of objects. A second PET experiment, described below, was designed to overcome this difficulty.

(*b*) *Object-location memory:* Shifted *versus* Fixed array

In this study, modelled closely on the one by Owen *et al.* (1996) and illustrated in figure 2, an attempt was made to enhance activation in the hippocampal formation in two ways. A baseline visual discrimination task was incorporated (shown in figure 2*f*) which was without a mnemonic component, and which could be performed on the basis of object-feature cues alone, without reference to spatial cues. Subjects merely had to touch the leaf on each trial and disregard the hammer. Second, the object-location retrieval task was made more difficult by changing the absolute positions of the stimuli while maintaining constant spatial relations among the set of items. Before scanning, 12 subjects performed an encoding task similar to that of Owen *et al.* (1996), except that two featureless square landmarks were present in fixed locations on the screen during the encoding trials (figure 2*a*). Retrieval was then tested in four different scanning conditions. In the two *Shifted* conditions, the array, composed of the eight object drawings and the landmarks, effectively shifted position from trial to trial, although the individual elements maintained the same spatial relations to each other. In one of these conditions, the landmarks themselves were presented as cues to the configuration of the stimuli (figure 2*c*), whereas in the other *Shifted* condition, two other objects from the array served as cues (figure 2*e*). In the two *Fixed* retrieval conditions, the array was static, in the same position as during encoding. Once again, either the two landmarks (figure 2*b*) or two other objects (figure 2*d*) were also visible on any given trial.

In this brief report, no detailed account of the results of the various subtractions can be given. Instead, this paper focuses on the findings with respect to the hippocampal region. When activity in the *Visuomotor* control condition was subtracted from that in each of the *Retrieval* scans involving landmark cues, significant activation foci were observed in the right parahippocampal gyrus bordering on the hippocampus, as shown in coronal section in figure 4*a*,*b* for *Fixed* and *Shifted* landmarks, respectively. Thus this region appears to be involved in the retrieval of object-location information, regardless of whether the retrieval task emphasizes the position of objects relative to a fixed external reference frame, as in the *Fixed-array* tasks, or the location of objects relative to each other (as in the *Shifted-array with landmarks* task).

The introduction of the simple visuomotor baseline task failed to bring out any important contribution from the hippocampus itself to the retrieval of object-location information. Nor did hippocampal CBF increase disproportionately in the *Shifted-array* compared with the *Fixed-array* conditions. Instead, subtraction of blood flow during *Fixed-array* from that during the *Shifted-array* analogues yielded significant activation in the right posterior inferotemporal cortex

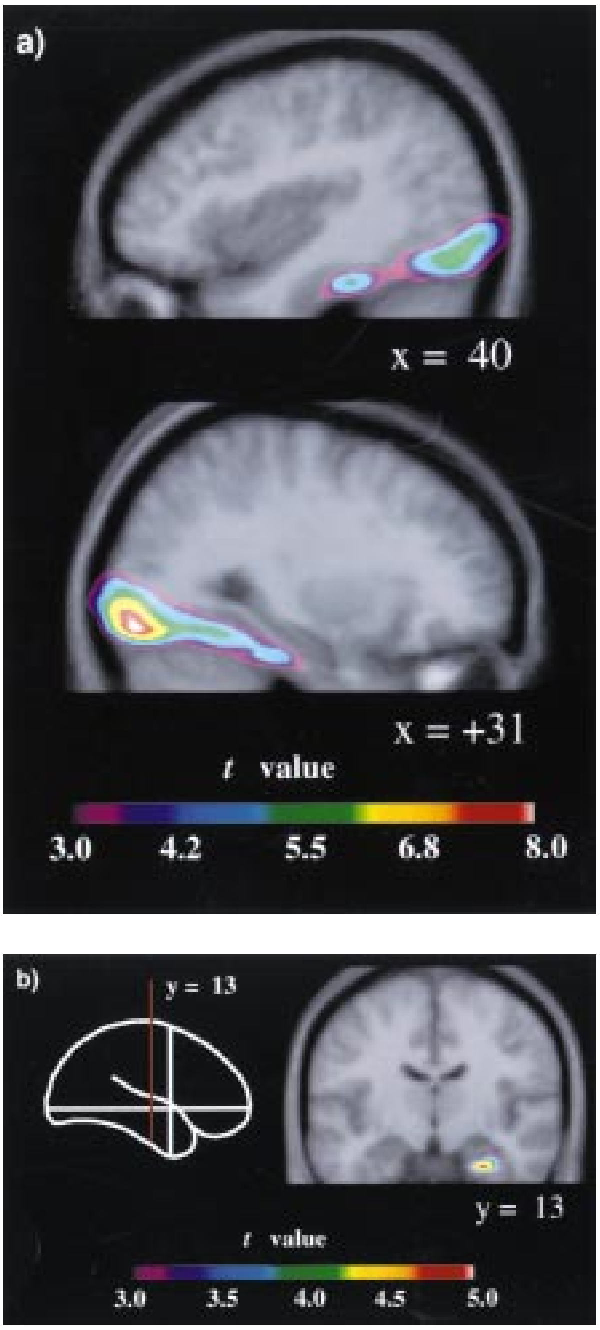

Figure 3. Object-location memory versus memory for simple location. In this and subsequent figures presenting imaging data, the averaged PET subtraction images are shown superimposed on the corresponding averaged MRI scans ($n = 12$), transformed into the standardized stereotaxic space of Talairach & Tournoux (1988). Subtraction of one condition from another yields focal changes in blood flow, which are shown as a t-statistic image, whose range is coded by the colour scale placed underneath each illustration. (*a*) *Encoding object-location* minus *Encoding location*. The sagittal sections illustrate the significant rCBF increases observed in inferior visual associative cortices, extending into the anterior fusiform gyrus, bilaterally. (*b*) *Retrieving object-location* minus *Retrieving location*. The coronal slice illustrates the significant rCBF increase observed in the right anterior parahippocampal gyrus in the region corresponding to the entorhinal cortex (Talairach coordinates: $x = 28$, $y = -13$, $z = -29$; $t = 4.89$). From Owen *et al.* (1996).

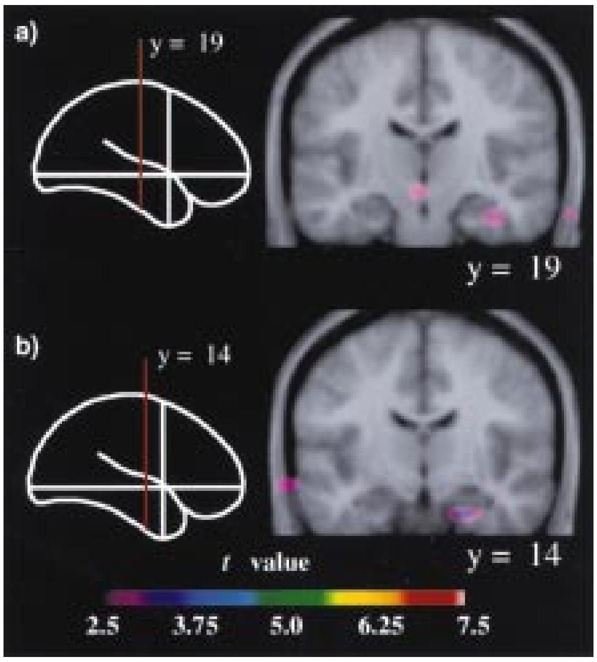

Figure 4. (*a*) *Fixed array with landmarks* minus *Visuomotor control*. This coronal section illustrates the significant rCBF increase observed in the right anterior parahippocampal gyrus (Talairach coordinates: $x = 36$, $y = -19$, $z = -23$; $t = 3.31$). The other two activation foci observed in this image are artefactual. (*b*) *Shifted array with landmarks* minus *Visuomotor control*. This coronal section illustrates the significant rCBF increase observed in the right hippocampus and for parahippocampal gyrus (Talairach coordinates: $x = 21$, $y = -14$, $z = -27$; $t = 3.54$).

(Brodmann's area 37), as shown in figure 5. Thus some lateralization of visual memory function within the neocortex was observed, a finding in accordance with a recent PET study by Moscovitch *et al.* (1995).

4. DISCUSSION

These findings as a whole point to a strong hemispheric asymmetry in the processes mediating memory for the location of objects. Surgical excision of the right medial temporal region, but not of the left, impaired the delayed recall of the locations of real objects in an array, in both single- and multi-trial studies, a result consonant with the authors' own earlier findings for other spatial-memory tasks, as well as with a recent study by Abrahams *et al.* (1997). A similar emphasis on the right hemisphere emerged from the two PET experiments in normal volunteer subjects, where activation was observed consistently in the right anterior parahippocampal gyrus, probably corresponding to entorhinal cortex, during retrieval of information about the location of objects on a computer screen, with no corresponding activation in the left hemisphere.

As Owen *et al.* (1996) have emphasized, the entorhinal area occupies a pivotal position within the hippocampal system (Amaral *et al.* 1995); it is known that in the monkey selective lesions of entorhinal and adjacent perirhinal cortex impair learning and memory for both objects and locations (Murray & Gaffan 1993; E. A. Murray, personal communication).

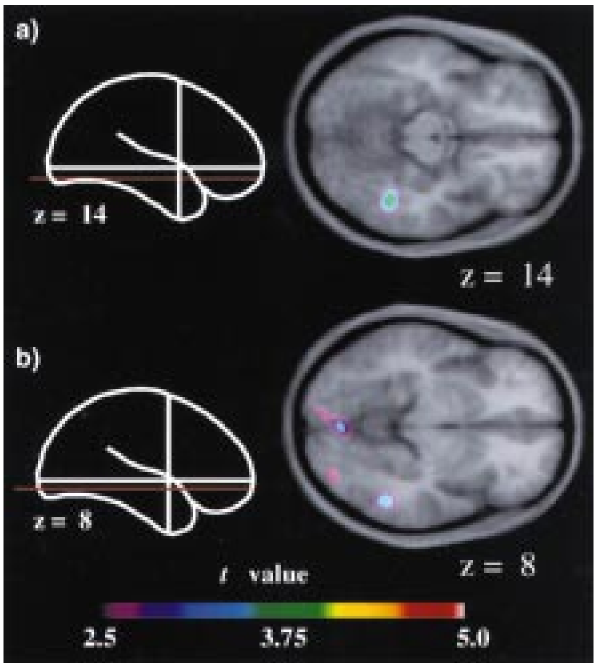

Figure 5. Object-location memory: shifted array versus fixed array. Significant rCBF increases occur in the two higher-order subtractions. (*a*) The significant rCBF increase observed in the right posterior inferotemporal cortex (BA 37) in the *Shifted array with landmarks* minus *Fixed array with landmarks* subtraction (Talairach coordinates: $x = 44$, $y = -45$, $z = -14$; $t = 3.99$). (*b*) The significant rCBF increase observed in the right posterior inferotemporal cortex (BA 37) in the *Shifted array with objects* minus *Fixed array with objects* subtraction (Talairach coordinates: $x = -51$, $y = -50$, $z = -8$; $t = 3.53$).

Furthermore, single-cell recording studies in the monkey have identified entorhinal neurones that respond selectively to objects (Quirk *et al.* 1992; Suzuki *et al.* 1995) and to a combination of both (Rolls *et al.* 1989). On the basis of studies in the rat, Eichenbaum & Bunsey (1995) have proposed that the parahippocampal region (including the entorhinal cortex) has the capacity to hold stimulus representations for extended periods of time, and that in so doing, it could combine simultaneously occurring stimuli into associated representations in memory (Gluck & Meyer 1995). It may be that object–place associations are a special instance of this.

Whereas the work reported here provides strong evidence for a contribution from the right parahippocampal-gyrus region to memory for object location, in neither of the PET studies could any clear activation in the hippocampus itself be elicited, despite the introduction of an ostensibly non-spatial baseline task in the second study. It seems possible, therefore, that the object-location memory task, at least in its two-dimensional computerized form, was too static to provoke increased blood-flow in the hippocampus itself, whereas tasks with a more navigational component may do so (Morris *et al.* 1982; Maguire *et al.* 1996). Against this interpretation, Aguirre *et al.* (1996) present evidence from a functional magnetic resonance imaging study, showing medial temporal-lobe activity confined to the parahippocampal gyri, and not involving

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the hippocampus itself, during the learning and recall of topographical information. It is clear that more work needs to be done to delineate the role of the human hippocampus in spatial learning and spatial memory.

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